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A non-compulsory stewardship programme for the management of antifungals in a university-affiliated hospital

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Abstract

Antimicrobial stewardship programmes promote excellence in the use of antimicrobials by selecting the appropriate antimicrobial agent and the correct dose, route of administration and duration of treatment. However, there is limited experience with such programmes targeting antifungal treatments. We present the results of a non-compulsory programme for the control of antifungals. For 12 months, prescriptions of oral voriconazole or intravenous voriconazole, caspofungin and liposomal amphotericin B were reviewed, and non-compulsory recommendations were made. The incidence and outcome of fungal infections were examined. The results for the dispensed defined daily doses (DDDs) and expenditure on antifungals were compared with those for the previous 12 months. The number of antifungal treatments reviewed was 662. A recommendation to change treatment was made in 29% of the cases, including a change from intravenous to oral treatment (15%), cessation of antifungal treatment (8%), and a change to fluconazole (6%). The DDDs of intravenous voriconazole and caspofungin were reduced by 31.4% and 20.2%, respectively. The DDDs of oral voriconazole and dispensed vials of liposomal amphotericin B were increased by 8.2% and 13.9%, respectively. Expenditure on antifungals was reduced by US$370681.78 (11.8% reduction). The programme was not related to significant increases in the incidence of candidaemia, percentage of persistent/relapsing candidaemia cases, percentage of fluconazole-resistant *Candida* species, incidence of infections by filamentous fungi, or 12-month mortality in patients with filamentous fungal infections. In conclusion, a stewardship programme targeting antifungals achieved a reduction in antifungal expenditure without reducing the quality of care provided.

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Introduction

Inappropriate use of antifungals contributes to the global increase in antifungal resistance, and may lead to a variety of adverse outcomes, including unnecessary exposure to drugs and increased costs [1,2]. The prompt initiation of effective antifungal therapy reduces patient mortality. However, the indiscriminate application of risk factor-based prediction models leads to a massive increase in the number of unnecessarily treated patients [3]. New antifungals have slight differences in the spectrum of action, dose required, route of administration, and interactions with other drugs, which are difficult to manage by a non-fungal specialist [3]. Therefore, the need for stewardship programmes targeting antifungals has been raised [3,4].

Methods

Setting

The study was developed at the University Hospital 12 de Octubre, a 1300-bed hospital. A stewardship programme

focusing on antibiotics had been previously developed in our hospital [5]. The present study is an intervention study that used a non-randomized uncontrolled before–after methodology. The primary outcome of the study was a reduction in antifungal expenditure. No stewardship programme targeting antifungals existed in the hospital before the intervention. The protocol of this study was approved by the Clinical Investigation Ethics Committee. The study was supported by the hospital administration. The study was led by the Infectious Diseases Unit, and the Departments of Pharmacy, Microbiology and Intensive Care actively cooperated in study development. The intervention was developed in 2008–2009.

Programme description

The present programme was initiated in all departments of the hospital attending to adults. A member of the Infectious Diseases Unit (F.L.M.) was partially dedicated to this programme (*c.* 3 h every weekday). All prescriptions of antifungals were checked every working day. The following prescriptions were selected to be reviewed: (i) every new prescription; and (ii) prescriptions susceptible to modification or discontinuation according to the criteria of the investigator, taking into consideration the treatment indication. Antifungal treatments were identified by the computerized system of the Department of Pharmacy. The Infectious Diseases Unit and the Department of Microbiology held a meeting every day, at which every clinically relevant fungal isolate was reported. Furthermore, the treatment of the patients admitted to the Department of Haematology (22-bed ward), the Postsurgical Unit of the Department of Anaesthesiology (17-bed ward), and the Department of General Intensive Care Medicine (14-bed ward) was reviewed. Throughout the intervention period, every prescription of the following antifungals was reviewed: intravenous liposomal amphotericin B, intravenous caspofungin, and intravenous and oral voriconazole. The appropriateness of the antifungal treatment was personally discussed with the attending physician. Most of the cases resulted in oral recommendations. In cases where the responsible physician could not be contacted, a written recommendation could be left until personal contact could be made. Recommendations were made regarding the necessity for prescription of the antifungal drug, the route of administration, the dose of the drug, and the possibility of substitution with another antifungal drug. All of the recommendations were non-compulsory. The attitude of the physician in charge concerning the recommendation was checked 48 h later. Recommendations were based on the guidelines of the Infectious Diseases Society of America for the use of antimicrobial agents in neutropenic patients [6], for the treatment of intra-abdominal infections [7], and for diseases caused by *Aspergillus* [8] and *Candida* [9]. Only local antimicrobial prescription guidelines were available in the Postsurgical Unit. A special effort was made to substitute fluconazole for caspofungin or liposomal amphotericin B when fluconazole-sensitive *Candida* species were isolated, to stop the prescribed antifungal treatment when a *Candida* isolate was considered to be a colonizing organism (mainly isolates from respiratory samples), to change from intravenous to oral voriconazole when feasible, to stop empirical antifungal treatment when the patient was considered to no longer be at risk for this type of infection, and to stop prophylactic antifungal treatment when the patient was considered to be at low risk. The antifungal treatment of a single patient could be reviewed more than once.

Description of outcomes

The results of the intervention were compared with the results achieved in the hospital in the immediately preceding 12 months, which will be referred to hereafter as the pre-intervention period. The defined daily doses (DDDs) and antifungal expenses were provided by the Department of Pharmacy. A DDD of caspofungin was considered to be 50 mg, and a DDD of oral or parenteral voriconazole was considered to be 0.4 g [10]. As a DDD for liposomal amphotericin B has not been described [10], the 50-mg vial was taken as the unit. The expenses were based on the price paid by our hospital. This price may differ from the officially established price, owing to discounts negotiated with antifungal drug suppliers. All costs in Euros (Spanish currency) were converted to US dollars, taking into consideration the equivalence at the end of the intervention period (€1 = US$1.56). The antifungal expenditures 2 years and 3 years before the intervention period were also analysed. The Department of Microbiology provided the information about the number of blood cultures positive for *Candida*, and the percentage of *Candida* isolates resistant to fluconazole, during the intervention and the pre-intervention periods. Susceptibility to fluconazole was tested with a commercially prepared dried colorimetric microdilution panel (Sensititre YeastOne; Trek Diagnostic Systems Ltd., East Grinstead, UK). The yeast was considered to be susceptible when the MIC of fluconazole was ≤8 mg/L. Relapsing and persisting candidaemia were analysed together for the purpose of this study. The definition of this joint concept was the growth of the same type of *Candida* species in a blood culture after 48 h and within 30 days of the first positive blood culture. Data on the number of patients admitted to the hospital, in-hospital mortality, average length of stay and number of days of hospitalization were provided by the administration of the hospital. The following infections caused by filamentous fungi throughout the intervention and the pre-intervention periods were

identified in the computerized registry of the hospital according to the standardized International Classification of Diseases (ICD-10) [11]: aspergillosis (B44), zygomycosis (B46), other mycoses (B48), and unspecified mycosis (B49). Patients were retrospectively diagnosed with invasive fungal diseases if they could be included in the categories of probable or proven infection [12]. A comparison of the incidence of candidaemia, percentage of relapsing/persisting candidaemia, percentage of candidaemia caused by fluconazole-resistant yeasts, incidence of infections caused by filamentous fungi and 12-month mortality in patients diagnosed with filamentous fungi infection throughout the intervention and the pre-intervention period was used as a marker of the quality of the medical care provided.

Statistical analysis

Continuous variables were expressed as the mean and standard deviation for those with a normal distribution. Categorical variables were expressed as percentages. Student's unpaired *t*-test was used to compare continuous variables, and the chi-square or Fisher exact test was applied to compare proportions when appropriate. All statistical tests were two-tailed. A p-value of <0.05 was considered to be statistically significant.

Results

Throughout the intervention period, a total of 5291 days on antifungal treatment were detected (Table 1), and 662 treatments were considered to be susceptible for review. The Intensive Care and Postsurgical Units were the departments with the highest number of reviewed treatments (38.7%). In >50% of the cases, treatments were active in targeting *Candida* species, followed by treatments targeting *Aspergillus*; both fungi were the target of >90% of the prescriptions. The most frequent indication for the drugs was the treatment of confirmed infections (Table 1). In 71% of the cases, the prescription made by the treating physician was considered to be correct. For 29% of the treatments, the following recommendations were made: in 15% of cases, the recommendation was to change from intravenous to oral treatment; in 8% of cases, the recommendation was to stop the administration of the antifungal; and in 6% of cases, the recommendation was to substitute fluconazole for the prescribed antifungal. In only 1% of the cases was the recommendation not accepted (three in the Intensive Care Unit, two in the Haematology Unit, and two in the Internal Medicine Unit). A mean of 4.5 revisions per patient was made in patients with confirmed infections.

TABLE 1. Characteristics of reviewed antifungal treatments in the intervention period

	N (%)
Reviewed antifungal treatments	662 (100)
Hospital department	
Intensive Care and Reanimation Units	256 (38.7)
Haematology and Oncology	188 (28.4)
Surgical Departments	128 (19.3)
Medical Departments	90 (13.6)
Days on treatment with antifungals	
Voriconazole (IV)	458
Voriconazole (oral)	2152
Caspofungin	1815
Liposomal amphotericin B	866
Total number of days on antifungals	5291
Target of prescribed antifungal treatment	
Candida	342 (51.7)
Aspergillus	285 (43)
Zygomycosis	15 (2.3)
Others	20 (3)
Indication for an antifungal drug	
Prophylaxis	181 (27.3)
Empirical treatment	201 (30.4)
Treatment of confirmed infection	280 (42.3)
Type of recommendation	
Treatment considered correct	470 (71)
Change IV to oral treatment	99 (15)
Cessation of treatment	53 (8)
Change to fluconazole	40 (6)
Recommendation not accepted	7 (1)

IV, intravenous.

Throughout the pre-intervention and the intervention periods, there were only slight changes in the mean price paid by the hospital for the different antifungals (Table 2); the price of a DDD of intravenous voriconazole and the price of a 50-mg vial of liposomal amphotericin B were the same in both periods. There was a reduction in the price of a DDD of caspofungin during the intervention period (0.11% reduction, equivalent to US$0.83 per dispensed DDD). There was a 3.39% increase in the mean price of oral voriconazole (US$3.79 per consumed DDD). The differences in the numbers of prescribed DDDs or vials of antifungals were analysed (Table 2), and important reductions in the prescribed doses of intravenous voriconazole and caspofungin were noted (31.4% and 20.2% reduction, respectively). In contrast, there was a 13.9% increase in the number of dispensed vials of liposomal amphotericin B and a 8.2% increase in the number of dispenses doses of oral voriconazole. Global expenditure on the four types of antifungal drug was US$3129387.34 in the pre-intervention period, in contrast to US$2758705.56 in the intervention period, resulting in a global reduction in antifungal costs of 11.84% and a cost saving of US$370681.78.

Fungal infections were examined to verify the quality of care provided (Table 3). The numbers of episodes of candidaemia were 69 in the pre-intervention period and 52 in the intervention period. There was no increase in the percentage

TABLE 2. Comparison of dispensed antifungals and their cost between the pre-intervention and intervention periods

	Mean cost of an individual DDD[a] (US$)			Dispensed DDD per 10^5 days of hospitalization[a]			Cost of antifungal treatment (US$)		
	Pre-intervention period	Intervention period	Change between periods (%)	Pre-intervention period	Intervention period	Change between periods (%)	Pre-intervention period	Intervention period	Change between periods (%)
Voriconazole (IV)	432.9	432.9	0	246.14	168.77	− 31.4	331 210.11	224 239.08	− 32.3
Voriconazole (oral)	111.96	115.75	+ 3.39	666.66	721.82	+ 8.2	231 997.3	256 460.88	+ 10.5
Caspofungin	728.88	728.05	− 0.11	822.70	656.82	− 20.2	1 863 765.88	1 467 699.48	− 21.2
Liposomal amphotericin B	187.11	187.11	0	1238.72	1411.06	+ 13.9	702 414.05	810 306.12	+ 12.5
Global							3 129 387.34	2 758 705.56	− 11.8
							Global saving: US$370 681.78		

DDD, defined daily dose; IV, intravenous.
[a]Dispensed in 50-mg vials in the case of liposomal amphotericin B.

of persisting or relapsing episodes of candidaemia. There was no increase in the percentage of episodes of candidaemia caused by fluconazole-resistant species. *Candida albicans* was the species most frequently isolated in blood cultures in both periods, followed by *Candida parapsilosis* (Table 3). The number of episodes of infection by filamentous fungi was 18 during the pre-intervention period, including ten episodes of aspergillosis, two episodes of pulmonary aspergillomas, five episodes of zygomycosis, and one episode of infection by *Cladosporium macrocarpum*. The number of filamentous fungal infections was ten during the intervention period, including eight episodes of aspergillosis, one episode of zygomycosis, and one episode of scedosporiosis. The difference was not significant (Table 3).

There was a 13.7% increase in expenditure between the third year before and the second year before the intervention periods (from US$2 300 288 to US$2 614 538). There was a 19.7% increase in expenditure between the second year before the pre-intervention period and the pre-intervention period itself (US$2 614 538 to US$3 129 387). In contrast, this trend was reversed by an 11.8% reduction in expenditure between the pre-intervention period and the intervention period (Table 3; Fig. 1).

Discussion

The appropriate use of antimicrobials has the potential to improve efficacy, reduce treatment-related costs, minimize drug-related adverse events, and limit the potential for emergence of antimicrobial resistance [13]. Recently published guidelines on antimicrobial stewardship programmes have raised the importance of having an infectious diseases specialist as a core member of the team [14].

Most decisions on antifungal prescriptions are made by physicians who are experts in their own field, but who do not necessarily have the expertise required to make informed choices in the prescription of antifungals. More than half of the prescriptions were made in the Departments of Haematology, Oncology and Intensive Care. In cases where a stewardship programme cannot be developed for the whole hospital, these departments should be the preferred targets.

TABLE 3. Comparison of fungal infections between the pre-intervention and intervention periods

	Pre-intervention period	Intervention period	p
Patients admitted to the hospital	26 996	26 991	
Total number of days of hospitalization	310 803	306 932	
Episodes of candidaemia	69	52	
Episodes of candidaemia per 10^3 hospital admissions	2.55	1.93	NS
Episodes of candidaemia per 10^4 days of hospitalization	2.22	1.92	NS
Candida albicans, *n* (%)	31 (45)	20 (38)	NS
Candida parapsilosis, *n* (%)	21 (30)	19 (36)	NS
Candida glabrata, *n* (%)	10 (13)	12 (23)	NS
Candida tropicalis, *n* (%)	5 (7.5)	1 (2)	NS
Candida krusei, *n* (%)	2 (3)	0 (0)	NS
Episodes of relapsing/persisting candidemia, *n* (%)	16 (24)	10 (19)	NS
% of candidaemia caused by fluconazole-resistant *Candida* species	4.7	5.3	NS
Episodes of filamentous fungal infections	18	10	
Episodes of filamentous fungal infections per 10^3 hospital admissions	0.67	0.37	NS
Episodes of filamentous fungal infections per 10^4 days of hospitalization	0.58	0.32	NS
12-month mortality in patients with the diagnosis of filamentous fungal infection, *n* (%)	9 (50)	5 (50)	NS

NS, not significant.

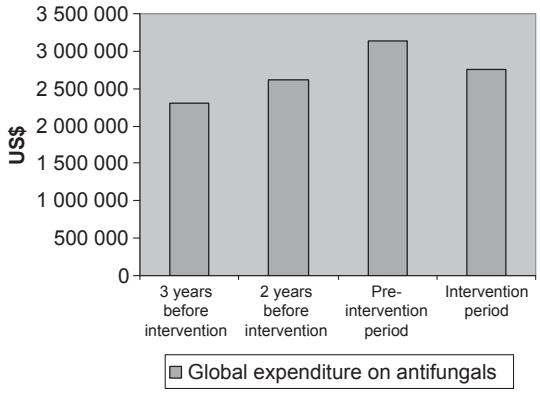

FIG. 1. Global economic results. Antifungal expenses (US$) in 12-month periods.

An acceptance of recommendations by physicians in charge of the patients can be challenging if there is a perceived loss of autonomy in clinical decision-making [13]. One of the strengths of our programme was that the recommendations were voluntary rather than mandatory. One of the reasons for the success of our programme was that the recommendations were personally made to the physician in charge. It is plausible that the effect of the programme extended beyond the controlled treatments; the reduction in prescriptions could be explained, in part, by the spontaneous initiative of treating physicians in the restriction of antifungals as part of the 'pleiotropic' effect of the programme. There was a progressive increase in antifungal expenditure in the years preceding the intervention. With the developed programme, this trend was not only stopped, but also reversed (Fig. 1). As the only cost of the programme was the part-time workday dedicated by the main investigator, its development was cost-effective.

During the intervention period, there was a reduction in the prescription of intravenous voriconazole that could, in part, be explained by a change in the prescription from intravenous to oral treatment. This change is reasonable, and takes into consideration the excellent oral bioavailability of this drug [15]. Part of the counterbalance of this reduction was an increase in the prescription of oral voriconazole. The main component of the cost savings was the important reduction in the use of caspofungin. It is probable that this drug was used in a more restrictive way for empirical treatment or prophylaxis in patients with a low risk of *Candida* infection. There was an increase in the prescription of liposomal amphotericin B. As neutropenia episodes were not systematically monitored, a higher number of episodes during the intervention period in which the drug was used cannot be ruled out.

The quality of care provided must be an essential part of any antimicrobial stewardship programme. There was no change in the incidence of mould or yeast infections, and there was no change in disease prognosis.

Previous studies have found misuse of antifungals in 26.9% [16] and 74% [17] of cases. To the best of our knowledge, there is only one previous report of a stewardship programme targeting antifungals active against *Candida* [4]. The authors concluded that there was a reduction in the inappropriate use of antifungals against *Candida* from 71% to 24%. There is no previously reported experience on stewardship programmes targeting antifungals against filamentous fungi.

There are some limitations to our study that should be noted. The results obtained in the intervention period were compared with those of the previous 12 months; thus, a bias resulting from a change in the characteristics of the admitted patients cannot be ruled out. This is an intrinsic limitation of studies with this type of design. Another limitation is that the programme was restricted to specific types of antifungals. When the study was developed, the only equinocandin available in our hospital was caspofungin, and posaconazole was not in the formulary. Adverse effects of antifungals were not specifically assessed. It is reasonable to suppose that the reduction in the prescription of antifungals was accompanied by a reduction in adverse effects. The rate of re-admission was not assessed.

Hospitals interested in developing a similar programme should pay special attention to the assignment of an expert in fungal infections, generate tight relationships with departments using these drugs, perform an exhaustive search of prescriptions on antifungals, prepare for the delivery of personal recommendations about specific patients, and allow close feedback. Future studies should explore the possibility of developing antifungal stewardship programmes more easily, and maintaining them for extended periods of time.

In conclusion, in the present environment of complexity in the prescription of antifungals, the development of stewardship programmes for these drugs could be of key importance in optimizing antifungal use while reducing expenditure and without detrimentally affecting the quality of care provided.

Transparency Declaration

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